

Amended

Patricia Booker

DO/ EO WORKSHEET

Patent Application Specialist/ National Stage Division

U.S. Appl. No. 10562023

International Appl. No. PCT/EP2004/06534

Application filed by: ☐ 20 months ☒ 30 months

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Publication No.: WO2004/113564

Publication Language: ☐ English ☐ German ☐ Japanese ☐ Chinese ☐ Korean
☐ French ☐ Spanish ☐ Russian ☐ Other: _____

Publication Date: 29 Dec 2004

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Published: ☒ EP request

INTERNATIONAL APPLICATION PAPERS IN THE APPLICATION FILE:

- ☒ International Application (RECORD COPY)
- ☐ Article 19 Amendments
- ☐ PCT/PEA/409 IPR: ☐ EP ☐ JP ☐ SE ☐ AU
☐ US ☐ FR ☐ CN ☐ ES ☐ RU ☐ AT ☐ KR ☐ _____
- ☐ Annexes to 409
- ☒ PCT/ISA/237: ☐ EP ☐ JP ☐ SE ☐ AU
☐ US ☐ FR ☐ CN ☐ ES ☐ RU ☐ AT ☐ KR ☐ _____
☐ PCT/PEA/409 or PCT/ISA/237 was NOT AVAILABLE at the time of paralegal review

- ☐ PCT/IB/306
- ☐ Request form PCT/RO/101
- ☒ PCT/ISA/210 - Search Report: ☐ EP ☐ JP ☐ SE ☐ AU
☐ US ☐ FR ☐ CN ☐ ES ☐ RU ☐ AT ☐ KR ☐ _____ ☐ NONE
- ☐ Search Report References
- ☒ Priority Document (s) No. 1
☐ N/A
☐ Priority Document was NOT AVAILABLE at the time of paralegal review
- ☒ Other: B4B

RECEIPTS FROM THE APPLICANT (other than checked above):

- ☒ Basic National Fee (or authorization to charge) 22/6
- ☒ Description ☒ Claims ☒ Abstract
- ☒ Drawing Figure(s) - (# of drwgs. 1)
- ☐ Translation of Article 19 Amendments
☐ entered ☐ not entered:
☐ not a page for page substitution
☐ replaced by Article 34 Amendment
- ☐ Annexes to 409
☐ entered ☐ not entered:
☐ not a page for page substitution
☐ no translation ☐ other: _____
- ☐ Application Data Sheet
- ☐ Power of Attorney
- ☐ Change of Address

- ☒ Preliminary Amendment(s) Filed on:
1. ☐ same as 371 request date 2. _____ 3. _____
- ☒ Information Disclosure Statement(s) Filed on:
1. ☐ same as 371 request date 2. _____ 3. _____
- ☒ Assignment Document (forwarded to Assignment Branch)
- ☐ Assignee Statement Under 37 CFR 3.73(b)
- ☐ Assignee PG Publication Notice
- ☐ Substitute Specification Filed on:
1. ☐ same as 371 request date 2. _____ 3. _____
- ☒ Verified Small Status Statement
- ☒ Oath/Declaration (executed)
- ☐ Oath/Declaration ☐ unsigned ☐ no citizenship ☐ other
- ☒ DNA Diskette ☒ Sequence Listing 18 Dec 2007
- ☐ Other: _____

NOTES: ☐ I.A. used as Specification ☐ Other: _____

35 U.S.C. 371 - Receipt of Request (PTO-1390)

Date Acceptable Oath/Declaration Received

Date of Completion of requirements under 35 U.S.C. 371

Date of Completion of DO/EO 903 - Notification of Acceptance

Date of Completion of DO/EO 905 - Notification of Missing Requirements

Date of Completion of DO/EO 909 - Notification of Abandonment

Date of Completion of DO/EO 916 - Notification of Defective Response

Date of Completion of DO/EO 922 - Notification to Comply w/ Requirements for Patent Applications Containing Nucleotide and/or Amino Acid Sequence Disclosures

Date of Completion of DO/EO 923

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PATENT APPLICATION FEE DETERMINATION RECORD
Effective December 8, 2004

Application or Docket Number
10562023

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
U.S. NATIONAL STAGE FEES		
BASIC FEE		
EXAMINATION FEE		
SEARCH FEE		
FEE FOR EXTRA SPEC. PGS.	minus 100 =	/ 50 =
TOTAL CHARGEABLE CLAIMS	22 minus 20 = *	2
INDEPENDENT CLAIMS	6 minus 3 = *	3
MULTIPLE DEPENDENT CLAIM PRESENT	<input type="checkbox"/>	

SMALL ENTITY TYPE		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	150	OR	BASIC FEE	
EXAM. FEE	100		EXAM. FEE	
SEARCH FEE	200		SEARCH FEE	
X \$ 125 =			X \$ 250 =	
X \$ 25 =	50	OR	X \$ 50 =	
X \$ 100 =	300	OR	X \$ 200 =	
+ \$ 180 =		OR	+ \$ 360 =	
TOTAL	800	OR	TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2

CLAIMS AS AMENDED - PART II

	(Column 1)		(Column 2)	(Column 3)
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR
	Total	*	Minus	**
	Independent	*	Minus	***
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <input type="checkbox"/>			

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X \$ 25 =		OR	X \$ 50 =	
X \$ 100 =		OR	X \$ 200 =	
+ \$ 180 =		OR	+ \$ 360 =	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

	(Column 1)		(Column 2)	(Column 3)
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR
	Total	*	Minus	**
	Independent	*	Minus	***
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <input type="checkbox"/>			

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X \$ 25 =		OR	X \$ 50 =	
X \$ 100 =		OR	X \$ 200 =	
+ \$ 180 =		OR	+ \$ 360 =	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than '20', enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than '3', enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

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Amended

MULTIPLE DEPENDENT CLAIM
FEE CALCULATION SHEET
(FOR USE WITH FORM PTO-875)

SERIAL NO.

10/562023

FILING DATE

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1 st AMENDMENT		AFTER 2 nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1		1			
2						
3						
4		3				
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18	1		1			
19	1		1			
20	1		1			
21	1		1			
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TOTAL IND.	6	↓	6	↓		↓
TOTAL DEP.	16	←	16	←		←
TOTAL CLAIMS	22		22			

	AS FILED		AFTER 1 st AMENDMENT		AFTER 2 nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						
52						
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100						
TOTAL IND.		↓		↓		↓
TOTAL DEP.		←		←		←
TOTAL CLAIMS						

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference P1156PC00	FOR FURTHER ACTION	See item 4 below
International application No. PCT/EP2004/006534	International filing date (<i>day/month/year</i>) 17 June 2004 (17.06.2004)	Priority date (<i>day/month/year</i>) 20 June 2003 (20.06.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant EPIGENOMICS AG		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|---|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the report |
| <input checked="" type="checkbox"/> | Box No. II | Priority |
| <input type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> | Box No. VI | Certain documents cited |
| <input type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input checked="" type="checkbox"/> | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Date of issuance of this report 03 January 2006 (03.01.2006) Authorized officer <div style="text-align: center; font-weight: bold; font-size: 1.2em;">Agnes Wittmann-Regis</div> Telephone No. +41 22 338 89 70
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PATENT COOPERATION TREATY

REC'D 22 NOV 2004

WIPO

PCT

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

29/12

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/006534

International filing date (day/month/year)
17.06.2004

Priority date (day/month/year)
20.06.2003

International Patent Classification (IPC) or both national classification and IPC
C12Q1/68, C07H21/00, A61K31/712

Applicant
EPIGENOMICS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Tudor, M

Telephone No. +49 89 2399-7709



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/006534

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☒ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☒ in written format
☒ in computer readable form
 - c. time of filing/furnishing:
☒ contained in the international application as filed.
☒ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/006534

Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-22
	No: Claims	
Inventive step (IS)	Yes: Claims	1-22
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-19,22
	No: Claims	20,21

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Cited documents

- 1.1 The documents mentioned in this written opinion are numbered as in the International Search Report i.e. D1 corresponds to the first document of the search report etc.

2. Novelty (Articles 33(2) PCT)

- 2.1 The present application satisfies the criterion set forth in Article 33(2) PCT because the subject matter of claims 1-22 is new in respect to the prior art as defined in the regulations (Rule 64(1)-(3) PCT).
- 2.2 None of the available prior art documents disclose the use of triplex forming oligonucleotides in a method for detecting methylated cytosines. Consequently, the subject-matter of claim 1 appears to be novel (Article 33(2) PCT).
- 2.3 Claims 2-17 are dependent on claim 1 and, as such, also meet the requirements of the PCT with respect to novelty (Article 33(2) PCT).
- 2.4 Furthermore, the prior art does not disclose the subject-matter of independent claims 18-22. Therefore, said subject-matter must also be considered novel (Article 33(2) PCT).

3. Inventive step (Article 33(3) PCT)

- 3.1 The present application also satisfies the criterion set forth in Article 33(3) PCT because the subject matter of claims 1-22 involves an inventive step with respect to the available prior art (Rule 65(1)(2) PCT).
- 3.2 Document D1, which can be considered as the closest prior art to the subject-matter of claim 1, describes a method of detecting cytosine methylation by performing PCR on a DNA sample in which all non-methylated cytosines have been chemically modified to uracil. The difference between D1 and the subject-matter of claim 1 is that the applicants have used triplex forming oligonucleotides comprising chemically modified bases which can distinguish between methylated

and unmethylated cytosines to detect cytosine methylation. The apparent technical problem can therefore be considered as to provide an alternative method for distinguishing methylated DNA from unmethylated DNA. Although documents D2 and D3 describe stable DNA triplex formation using oligonucleotides containing derivatives of cytosine, in particular, N⁴-(3-acetamidopropyl)cytosine and N⁴-(6-amino-2-pyridinyl)deoxycytidine, there is no suggestion in said documents that the therein described oligonucleotides would preferentially bind to unmethylated cytosines as opposed to methylated cytosines. Consequently, the solution to the apparent technical problem, as stated in claim 1, would not be obvious and would require inventive effort on behalf of the skilled person. Therefore, claim 1 appears to meet the requirements of Article 33(3) PCT.

3.3 Claims 2-17 are dependent on claim 1 and, as such, also meet the requirements of the PCT with respect to inventive step (Article 33(3) PCT).

3.4 The reasoning stated in item 3.2 above is also applicable *mutatis mutandis* to independent claims 18-22. Therefore, claims 18-22 also appear to be inventive (Article 33(3) PCT).

4. Industrial Applicability (Article 33(4) PCT)

4.1 Claims 20 and 21, as far as *in vivo* methods are concerned, can be considered as methods of treatment. For the assessment of claims 21 and 22 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

1. Claims 1-4, and 10-21 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, which merely

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2004/006534

amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.